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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,345	01/14/2004	Sudhir Agrawal	HYB-018US1	3490

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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,345	AGRAWAL ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,10-16,18,31,32,40,42,95,99 and 147-149* is/are pending in the application.

4a) Of the above claim(s) *3,5,10-16,18,32,40,42,95,99 and 147* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,31,148 and 149* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *March 11, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant has elected the invention of Group I, drawn to an immunomer compound comprising at least two oligonucleotides linked together, wherein Applicant has elected the oligonucleotide linkage species to be "iv", a sugar to a non-nucleotide linker and the "G" moiety species to be "2'-deoxy-7-deazaguanosine". However, upon further consideration, the Examiner has withdrawn the "G" species election requirement.

Election of Applicant's invention(s) was made without traverse.

Amendments

Applicant's response and amendments, filed February 10, 2009, to the prior Office Action is acknowledged. Applicant has cancelled Claims 2, 4, 6-9, 17, 19-30, 33-39, 41, 43-94, 96-98 and 100-146, withdrawn Claims 3, 5, 10-16, 18, 32, 40 and 42, 95, 99 and 147, amended Claim 1, and added new claims, Claims 148-149.

Claims 3, 5, 10-16, 18, 32, 40, 42, 95, 99 and 147 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1, 31 and 148-149 are under consideration.

Priority

Applicant's claim for the benefit of a prior-filed parent provisional application 60/440,587 filed on January 16, 2003 under 35 U.S.C. 119(e) is acknowledged.

Accordingly, the effective priority date of the instant application is granted as January 16, 2003.

Information Disclosure Statement

Upon review of the prosecution history, the examiner noticed that the IDS filed March 11, 2004 does not list the publication dates of citations A1-A7. The examiner has entered the publication dates onto the IDS to correct this error.

The signed and initialed PTO Forms 1449 are mailed with this action.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the February 10, 2009 response will be addressed to the extent that they apply to current rejection(s).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. **The prior rejection of Claims 1 and 31 under 35 U.S.C. 103(a)** as being unpatentable over Kandimalla et al (Bioorganic & Medicinal Chem. 9:807-813, 2001; *of record in IDS) in view of Kandimalla et al (WO 02/26757; *of record in IDS) and Simmonds et al (WO 99/06422, U.S. equivalent 6,444,682) **is withdrawn** because upon further consideration of the claimed invention as a whole, the Examiner finds that while the prior art teaches a plurality of species within an genus of structurally related nucleoside bases (Simmonds et al, 1999), and that it is routine to screen a plurality of structurally related nucleoside base species to identify those species that have the desired activity in the context of a CpG-containing oligonucleotide (Kandimalla et al, 2001), neither Kandimalla et al nor Simmonds et al teach the instantly claimed structure, a CpG-containing oligonucleotide in which the cytosine base in the CpG motif is substituted for a 1-(2'-deoxy-β-D-ribofuranosyl)-2-oxo-7-deaza-8-methyl-purine.

2. **Claims 1, 31 and 148 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Yu et al (Bioorg. & Med. Chem. 10:2585-2588, 2000; *of record in IDS) in view of Kandimalla

et al (Bioorganic & Medicinal Chem. 9:807-813, 2001; *of record in IDS) and Liu et al (J. Mol. Biol. 308(3):465-475, 2001).

This is a new rejection.

Determining the scope and contents of the prior art.

Yu et al teach an immunomer compound comprising at least two phosphorothioate (PS) oligonucleotides linked at their 3' ends, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprises an immunostimulatory C(ps)G dinucleotide motif, whereupon the PS-oligos that have their 3' ends blocked are very resistant to exonucleases and have higher immunostimulatory activity than non-linked oligos (pg 2587, Figures 2-3).

Yu et al do not teach the immunomer compound comprises a psC*psG dinucleotide motif illustrated in Figure 24 of the instant application. However, at the time of the invention, Kandimalla et al taught the synthesis of phosphorothioate CpG immunostimulatory oligonucleotides comprising a psC*psG dinucleotide motif, wherein the C* moiety represents a monocyclic or bicyclic cytosine analogue (pg 808, Figures 1 and 2) and the "G" moiety represents a guanosine or guanosine analogue, including 2' deoxyguanosine, 2'-deoxy-7-deazaguanosine, and other non-natural purine nucleosides (pg 809, Figure 3).

Neither Yu et al nor Kandimalla et al teach the cytosine is substituted for 2-oxo-7-deaza-8-methyl-purine (also known in the art as pyrrolocytosine). However, at the time of the invention, Liu et al taught the substitution of a cytosine for pyrrolocytosine in nucleic acid oligonucleotides.

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in functional equivalents and analogues of nucleic acids and

chemical synthesis of immunostimulatory oligonucleotides. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to substitute a first bicyclic non-natural cytosine analogue as taught by Kandimalla et al with a second bicyclic non-natural cytosine analogue having the structure shown in Figure 24 (Liu et al) with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, the prior art recognized that the P-base pyrrolocytosine (a.k.a. 2-oxo-7-deaza-8-methyl-purine) is a cytosine analogue. An artisan would be motivated to substitute a first bicyclic non-natural cytosine analogue as taught by Kandimalla et al with a second bicyclic non-natural cytosine analogue having the structure shown in Figure 24 because Liu et al teach that pyrrolocytosine is advantageous because it is intrinsically highly fluorescent, with excitation and emission maxima far from those of DNA and protein, making it ideal for probing protein-nucleic acid interactions (pg 466, col. 2, last ¶), i.e. the structure-immunostimulatory activity relationships of CpG oligos and the intracellular receptor/protein to which CpG oligos bind, triggering the immune cascade (Kandimalla), thereby providing the artisan a tool with which to study the not well-understood mechanism (Kandimalla) by which CpG oligonucleotide structures effect immunostimulatory activity.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

3. **Claim 149 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Yu et al (Bioorg. & Med. Chem. 10:2585-2588, 2000; *of record in IDS) in view of Kandimalla et al

(Bioorganic & Medicinal Chem. 9:807-813, 2001; *of record in IDS) and Liu et al (J. Mol. Biol. 308(3):465-475, 2001), as applied to Claims 1, 31 and 148 above, and in further view of Hutcherson et al (U.S. Patent 5,663,153).

Neither Yu et al, Kandimalla et al nor Liu et al teach an immunomer compound consisting essentially of phosphorothioate internucleoside linkages. However, at the time of the invention, Hutcherson et al disclose immunostimulatory oligonucleotides consisting essentially of phosphorothioate internucleoside linkages.

It would have been obvious to modify the immunostimulatory oligonucleotides comprising phosphorothioate internucleoside linkages of Yu et al in view of Kandimalla et al and Liu et al to consist essentially of phosphorothioate internucleoside linkages as taught by Hutcherson et al with a reasonable expectation of success because Hutcherson et al successfully demonstrated that oligonucleotides consisting essentially of phosphorothioate internucleoside linkages possess immunostimulatory activity.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. **The prior rejection of Claims 1 and 31** on the ground of nonstatutory obviousness-type double patenting over Claims 37, 39, 40 and 52-59 of copending Application No. 10/279,684 (now U.S. Patent 7,276,489) in view of Simmonds et al (WO 99/06422, U.S. equivalent 6,444,682**) is withdrawn** because upon further consideration of the claimed invention as a whole, the Examiner finds that while the Simmonds et al teach a plurality of species within an genus of structurally related nucleoside bases, Simmonds et al does not immediately suggest the specific pyrrolocytosine nucleoside.

5. **The prior rejection of Claims 1 and 31** on the ground of nonstatutory obviousness-type double patenting over Claim 12 of copending Application No. 10/694,383 (U.S. 2004/0266710) in view of Simmonds et al (WO 99/06422, U.S. equivalent 6,444,682) **is withdrawn** because upon further consideration of the claimed invention as a whole, the Examiner finds that while the Simmonds et al teach a plurality of species within an genus of structurally related nucleoside bases, Simmonds et al does not immediately suggest the specific pyrrolocytosine nucleoside.

6. **The prior rejection of Claims 1 and 31** on the ground of nonstatutory obviousness-type double patenting over Claims 20-21 of copending Application No. 10/694,586 (U.S. 2006/0142224) in view of Simmonds et al (WO 99/06422, U.S. equivalent 6,444,682). **is withdrawn** because upon further consideration of the claimed invention as a whole, the Examiner finds that while the Simmonds et al teach a plurality of species within an genus of structurally related nucleoside bases, Simmonds et al does not immediately suggest the specific pyrrolocytosine nucleoside.

7. **The prior rejection of Claims 1 and 31** on the ground of nonstatutory obviousness-type double patenting over Claims 1-5, 16, 21-23 of copending Application No. 10/925,873 **is withdrawn** in light of the cancellation of the co-pending claims (amendment filed September 25, 2008).

8. **Claim 1 stands provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claim 1 of copending Application No. 10/361,111 (U.S. 2004/0156825).

Note: A Notice of Allowance of Claim 1 of 10/361,111 was mailed December 21, 2007.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunomers having at least two oligonucleotides linked together by a non-nucleotidic linker, wherein the internucleoside linkage is modified, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside. Thus, although the subject matter is recited using different terms, the composition(s) of the instant claim(s) is reasonably embraces and anticipates the composition(s) recited in the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

9. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claim 18 of copending Application No. 10/865,245.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside.

The claims are drawn to an immunostimulatory oligonucleotide compound comprising a "CpG" motif, wherein the "C" moiety is a non-natural pyrimidine and the "G" moiety is a natural or non-natural pyrimidine nucleoside, wherein the immunostimulatory oligonucleotides may be joined by 3' to 3' linkages. Thus, instantly claimed immunomer composition(s) are reasonably embraced by immunostimulatory oligonucleotide(s) of the copending application. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

10. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 11-13 and 16 of copending Application No. 11/153,054.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside.

Because the claims of copending Application No. 11/153,054 recite generically "CpG, C*pG, C*pG* and CpG*", the Examiner has looked to the specification for definitions of the "C" and "G" moieties so as to better understand the invention. The specification discloses that C* is… 1-(2'-deoxy-β-D-ribofuranosyl)-2-oxo-7-deaza-8-methyl-purine, and that G* is… 2'-deoxy-7-deazaguanosine (pg 1, [0010]), wherein the non-nucleotidic linker may be a 3'-3' linkage (pg 3, [0032]). Thus, instantly claimed immunomer composition(s) anticipate immunostimulatory oligonucleotide(s) of the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

11. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 1 and 4 of copending Application No. 11/174,002 (U.S. 2006/0211641).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a natural or non-natural purine nucleoside.
Thus, instantly claimed immunomer composition(s) anticipate immunostimulatory oligonucleotide(s) of the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Response to Arguments

Applicant argues that Applicants will consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed, copending applications 10/361,111, 10/865,245, 11/153,054 and 11/174,002.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant has not filed a Terminal Disclaimer or taken any other action deemed necessary in the later filed, copending applications as it pertains to the instant application. The provisional nonstatutory obviousness-type double patenting rejections will be maintained until all claims have been deemed otherwise in condition for allowance or allowable.

Conclusion

12. No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure:

Krieg et al (U.S. 2004/0053880 A1) disclosed immunostimulatory nucleic acids comprising CpG motifs, wherein the cytosine may be substituted with a P-base [0094].

Fearon et al (U.S. Patent 7,255,868) disclosed immunostimulatory nucleic acids comprising CpG motifs, wherein the cytosine may be substituted with an isostructural bicyclic analog (col. 30, line 45-col. 31, line 40).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633

/Anne Marie S. Wehbé/
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